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EXAMINER	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 1203

Application Number: 10/044,807
Filing Date: January 11, 2002
Appellant(s): YU ET AL.

David Hibler
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed October 21, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

Appellant's brief includes a statement that there are no related appeals or interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The statement of the status of the amendments contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is substantially correct. However, it includes discussion of Applicant's deductions for the utility of the polypeptide encoded by the polynucleotide of SEQ ID NO: 1, which forms the basis of the instant rejection and will be addressed in the Response to Arguments section of this Answer.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is incorrect with regards to the presentation of Claim 2. It is noted that Claim 2 in Exhibit A of Applicant's amendment, received July 23, 2003, is also not correct.

The correct pending claims are:

1. An isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO : 1 .

2. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO : 2 .

3. An isolated expression vector comprising the nucleotide sequence of SEQ ID NO:1.

4. A host cell comprising the expression vector of claim 3. .

(9) Prior Art of Record

- Art cited in rejections.
- Venter et al., The sequence of the human genome. Science. 2001; 291(5507): 1304-51.
- GenBank Acc#NM_139238 Homo sapiens ADAMTS-like 1 (ADAMTSL1), transcript variant 1, mRNA.
- GenBank Acc#NM_052866 Homo sapiens ADAMTS-like 1 (ADAMTSL1), transcript variant 2, mRNA.
- AU-YOUNG, JANICE ET AL. USSN5817479 OCT-06-1998 NOVEL HUMAN KINASE HOMOLOGS.
- JACOBS, KENNETH ET AL USSN5654173 AUG-07-1997 SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM.
- STASHENKO, PHILIP ET AL USSN5552281 SEP-02-1996 HUMAN OSTEOCLAST-SPECIFIC AND -RELATED GENES
- YAN, CHUNHUA ET AL USSN6340583 JAN-22-2002 ISOLATED HUMAN KINASE PROTEINS, NUCLEIC ACID MOLECULES ENCODING HUMAN KINASE PROTEINS, AND USES THEREOF
- NCBI Single Nucleotide Polymorphism, www.ncbi.nlm.hig.gov/SNP/, March 1, 2001.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

Claims 1-4 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 1-4 are directed to isolated polynucleotides encoding a polypeptide as well as vectors and host cells comprising said polynucleotides. The specification discloses, that the claimed polynucleotides encode a protein, which shares structural similarities with animal proteases, and particularly matrix metalloproteases, zinc dependent metalloproteases, and collagenases (pg 2, lines 6-9). Based on structural similarity, the specification asserts that the claimed polynucleotides encode a novel human protein sharing sequence similarity with mammalian proteases (Title; pg 1, lines 10-13). The specification states that the sequence data indicate the encoded protein displays thrombospondin and disintegrin domains, and particular structural similarity to the ADAMTS family of metalloproteases (pg 17, lines 29). However, the specification also states that the encoded protein has similarity to receptor-linked phosphatases and membrane associated cell adhesion proteins (pg 18, line). Thus, a clear assertion for the utility of the recited proteins is not presented.

The alleged function for the claimed polynucleotides as encoding proteases is based solely on structural similarity (pg 2, lines 6-9; pg 17, lines 29). However, the specification fails to identify any specific protein, with any specific and substantial function, to which the instant protein, as set forth by SEQ ID NO: 2, is homologous. Sequence searches showed no consistent homology for the full-length SEQ ID NO: 2 with metalloproteases. One polynucleotide sequence showing high homology to SEQ ID NO: 1 (i.e. 98% over the full-length of SEQ ID NO: 1) encodes a protein of unknown function having a thrombospondin-like domain

(WO200121658-A1 SEQ ID NO: 18; Gene #8; p26-30 and Figs 4-5). A second polynucleotide sequence showing high homology to SEQ ID NO: 1 (i.e. 98% over the full-length of SEQ ID NO: 1) encodes a hypothetical protein from C. elegans of unknown function that is not a metalloprotease (WO200154474-A2 SEQ ID NO: 134; Gene #124; Table 1 p76 and Table 2 p226). A third protein, TANGO 224, has a thrombospondin domain but is not a metalloprotease (WO200039284-A1 SEQ ID NO: 224; Abstract and pages 52-56). Clearly, a specific and substantial or well-established utility for the polypeptide of SEQ ID NO: 2 cannot be deduced based on homology to known proteins.

There is no experimental evidence within the specification to support the assertion that the claimed polynucleotides encode any specific functional polypeptide. The biochemical characteristics of the protein set forth by SEQ ID NO: 2 are not disclosed. Furthermore, neither the substrates acted on, biochemical reactions mediated by, nor specific diseases caused by the polypeptide of SEQ ID NO: 2 are taught by the specification. The specification does teach that Applicant's novel human protein can be expressed in numerous tissues, cell types, and developmental stages (pg3, line 30 -pg4, line 6). This ubiquitous expression of the instant protein sheds no light on its possible function. The specification also states that "...an individual suspected of carrying, or known to carry, a mutant NHP allele..." may be "... (e.g., a person manifesting a NHP-associated phenotype such as, for example, obesity, high blood pressure, connective tissue disorders, infertility, etc.)..." (pg 14, lines 10-14). Such a listing of diseases that the polypeptide of SEQ ID NO: 2 may be associated with fails to reveal to the public a specific function for said polypeptide. The specification fails to positively identify a single condition from the large laundry list with which the gene/protein is clearly associated; "may be"

is not the same as "is". The specification merely provides unsupported speculation as to numerous conditions that a human gene might be involved in, but leaves the determination of which of these is correct for others to figure out.

As stated in the specification, the proposed utilities for the polynucleotides encoding SEQ ID NO: 2 are: identification of coding regions and exon splice junctions; in restriction fragment length polymorphism analysis and forensics; identification of compounds that modulate the polypeptide of SEQ ID NO: 2 (pg 3, lines 1-15); microarrays, or other assay, to screen genetic material from patients; identification of mutations associated with SEQ ID NO: 2; diagnostic assays; preparation of anti-sense oligonucleotides derived from SEQ ID NO: 2; hybridization assays; library screening; characterization of genomic clones; PCR; restriction fragment length polymorphism analysis; isolation of full-length cDNA; preparation of fusion proteins; preparation of antibodies; as therapeutics (page 8-16); analysis of protein evolution; and preparation of transgenic animals (page 18-21). None of these uses is specific to the recited polynucleotides; each method could utilize any polynucleotide or is only a way to further characterize the recited polynucleotides and the encoded protein. For example, the presence of polymorphisms in human DNA is well established and virtually any locus on a human chromosome will exhibit one or more polymorphisms. Applicants have not identified any particular reason for use of this particular DNA in screening genetic material from patients. Applicants have also not identified any particular reason for use of this particular polynucleotide as a therapeutic for the treatment of a human disease and no specific human diseases have been shown in the specification to be associated with or correlated with alterations in this particular polynucleotide. Likewise, applicants have not identified any particular reason for using this

polynucleotide for preparing fusion proteins or antibodies. Since, function/activity of the instant protein is not known, these utilities recited in the specification are not substantial since they will require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. See e.g., Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966).

The instant situation is analogous to the lack of substantial utility examples provided by MPEP § 2107.01 in that basic research is required to study the properties of the claimed polynucleotides and the corresponding polypeptide as well as the mechanisms in which the claimed polynucleotides are involved. In addition, while one could argue that some of the recited uses, such as being a probe to be used in microarrays or in mapping of nucleotides in a particular chromosome would not require further research to practice, it is noted that these uses are not specific, due to the fact that all other human polynucleotides can be used as probes in microarrays or in mapping of nucleotides in the chromosome. Since the instant specification does not disclose a credible, specific and substantial "real world" use for the polynucleotide of SEQ ID NO: 1 or a polynucleotide encoding the polypeptide of SEQ ID NO: 2, then the claimed invention as disclosed does not meet the requirements of 35 U.S.C. §101 as being useful. Therefore, Claims 1-4 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claim Rejections - 35 USC §112, First Paragraph

Claims 1-4 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantial and specific asserted utility or a well

established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(11) Response to Argument

A. Do Claims 1-4 lack a patentable utility?

In support of their request for withdrawal of the rejection of Claims 1-4 under 35 U.S.C. 101, Appellants provide the following arguments.

(1) In the instant Brief, Appellants argue, as they did in both the Response to the First Action and in the Response to the Final Action, that the present nucleic acid sequences have use in forensic analysis and that said use is a specific and substantial utility based on the following. "As described in the specification at page 18, lines 3-27, the present sequences define a number of coding single nucleotide polymorphisms - specifically: a C/G polymorphism at position 2361 of SEQ ID NO:1, which can result in an aspartate or glutamate at amino acid position 787 of SEQ ID NO: 2; a C/A polymorphism at position 2467 of SEQ ID NO: 1, which can result in a leucine or isoleucine at amino acid position 823 of SEQ ID NO:2; a C/A polymorphism at position 2613 of SEQ ID NO: l, both of which result in an isoleucine at corresponding at position 871 of SEQDNO:2; a C/T polymorphism at position 3141 of SEQ ID NO: l, both of which result in a serine at amino acid position 1047 of SEQ ID NO: 2; a G/T polymorphism at position 3225 of SEQ ID NO: 1, which can result in a glutamine or histidine at amino acid position 1075 of SEQ ID NO:2; a C/T polymorphism at position 3226 of SEQ ID NO:1, which can result in an arginine or tryptophan at amino acid position 1076 of SEQD NO:2; and an A/G polymorphism at position 4226 of SEQID NO:1, which can result in an aspartate or glycine at amino acid position

1409 of SEQ mNO:2. As such polymorphisms are the basis for forensic analysis, which is undoubtedly a "real world" utility, the presently claimed sequence must in itself be useful.

Appellants respectfully point out that the presently described polymorphisms are useful in forensic analysis exactly as they were described in the specification as originally filed-specifically, to distinguish individual members of the human population from one another based simply on the presence or absence of one or more of the described polymorphisms. The skilled artisan would be able to use the presently described polymorphisms in forensic analysis exactly as they were described in the specification as originally filed, without any additional research.

This is also not a case of a potential utility. Even in the worst case scenario, the described polymorphisms are each useful to distinguish 50% of the population (in other words, the marker being present in half of the population). Appellants respectfully point out that all that is required to support Appellants' assertion of utility is for the skilled artisan to believe that the presently described polymorphic markers could be useful in forensic analysis. The fact that forensic biologists use polymorphic markers such as those described by Appellants every day provides more than ample support for the assertion that forensic biologists would also be able to use the specific polymorphic markers described by Appellants in the same fashion. Therefore, the presently claimed sequence clearly has a substantial and well established utility.

The Examiner questioned this asserted utility, stating "the presence of polymorphisms in human DNA is well established and virtually any locus on a human chromosome will exhibit one or more polymorphisms which could be so used. This argument is flawed. Until a polymorphic marker is actually described it cannot be used in forensic analysis. The Examiner appears to be attempting to use the information presented for the first time by Appellants in the instant

specification as hindsight verification that the presently claimed sequence would be expected to have polymorphic markers.

Reply: Regarding the assertion that use of the polynucleotide of SEQ ID NO: 1 in forensic analysis is a specific and substantial utility, it is acknowledged that the use of polynucleotides in forensic analysis is a substantial utility. However, the use of the polynucleotide of SEQ ID NO: 1, or any polynucleotide encoding SEQ ID NO: 2, in forensic analysis is not a specific utility for the following reasons. Appellant's own argument provides insight: "...the presently described polymorphism would be used in forensic analysis for the exact same reason that any polymorphic marker would be so used-specifically, to specifically identify individual members of the human population based on the presence or absence of the described polymorphism" (pg 4, parg 4-pg 5, parg 1). The presence of polymorphisms in human DNA is well established; single nucleotide polymorphisms occur approximately once every 100 to 300 bases (NCBI Single Nucleotide Polymporphism, www.ncbi.nlm.hig.gov/SNP/, March 1, 2001). Therefore, virtually any gene on a human chromosome will exhibit one or more polymorphisms, which could be used for forensics. Thus, based on appellant's argument, any polynucleotide having a polymorphism, which is all or essentially all polynucleotides, has a specific and substantial utility in forensics. However, if every polynucleotide has the same utility, then clearly it is NOT a specific utility. Such an argument is analogous to any mouse, including a recombinant mouse, having utility as snake food (MPEP 2107.01).

It is acknowledged that forensic analysis of the target gene encoding the protein of SEQ ID NO: 2 cannot be performed with just any nucleic acid. However, Appellants have not identified any particular reason for use of a particular polymorphism in forensic analysis of the

target gene or any particular benefit that would derive from analysis of a polymorphism in the target gene. If further research were to show that the instant polymorphism is associated with a specific disease, then using the polynucleotide of SEQ ID NO: 1 to genetically screen for said disease would be a specific utility. However, such a utility is presently only potential, and not currently available in practical form.

(2) The Examiner seems to be confusing the requirements of a specific utility with a unique utility. The fact that other polymorphic markers have been identified in other genetic loci, or that the use of the presently described polymorphic markers will provide additional information concerning the prevalence of these markers in certain subpopulations, does not mean that use of the polymorphic markers identified by Appellants' in forensic analysis is not a specific utility.

If every invention were required to have a unique utility, the patent and Trademark Office would no longer be issuing patents on batteries, automobile tires, golf balls, golf clubs, and treatments for a variety of human diseases, such as cancer, just to name a few particular examples, because the utility of each of these compositions is applicable to the broad class in which each of these compositions falls. However, only the briefest perusal of virtually any issue of the Official Gazette provides numerous examples of patents being granted on each of the above compositions nearly every week.

Reply: Batteries, automobile tires, golf balls, golf clubs, and methods of treatment for a variety of human diseases each have a specific utility that is known to the public. All new patents issued for said products and methods are an improvement and/or variation on the well-established specific utility. A specific and substantial or well-established utility for an invention

is required for a patent, a unique utility is not required. For example, if a disease is known to be associated with more than one mutation of a single gene, more that one polynucleotide would have the specific, but not unique, utility of being used for screening for said disease.

Appellants have never been asked to identity a utility that is unique, i.e., not shared by any other compounds or compositions. Rather, Appellants have been required to identify a utility that is specific to the invention claimed, as opposed to one that would apply regardless of the specific properties of the claimed invention. See, e.g., Brenner, 383 U.S. at 534, 148 USPQ at 695 (An invention does not have utility sufficient to satisfy § 101 until it is "refined and developed" to the point of providing a specific benefit in currently available form.). An invention certainly can have a utility that is shared by other compound or compositions. On the other hand, not every utility will satisfy § 101, even if the utility is shared by a class of inventions. So while, a utility need not be unique to a claimed invention, it must nonetheless be specific, and in currently available form, in order to satisfy § 101. Here Appellants assert that the claimed polynucleotides can be used as a polymorphic marker in forensic analysis. However, any observed results of the presence or absence of the claimed polymorphism would have no meaning without additional knowledge of what the significance of this sequence variation is. The specification in effect discloses that the claimed products include a polymorphic site and those of skill in the art will figure out what to do with it. This utility is not substantial; it does not provide a specific benefit in currently available form.

(3) As the presently described polymorphisms are a part of the family of polymorphisms that have a well established utility, the Federal Circuit's holding in In re Brana, (34USPQ2d 1436 (Fed. Cir. 1995), "Brana") is directly on point. In Brana, the Federal Circuit admonished the

Patent and Trademark Office for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". The Federal Circuit is evidently using "utility" to refer to rejections under 3SU.S.C. 101, and is using "usefulness" to refer to rejections under 3SU.S.C. 112, first paragraph.

As discussed above, even if the use of these polymorphic markers provided additional information on the percentage of particular subpopulations that contain these polymorphic markers, this would not mean that "additional research" is needed in order for these markers to be used as they are presently described in the instant specification to be of use to forensic science. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue" not "Experimentation".

The Examiner further stated that "Applicants have not identified any particular reason for use of this particular polymorphism in forensic analysis or any particular benefit that would derive from analysis of this polymorphism". As clearly set forth above, Appellants respectfully point out that the presently described polymorphism are useful in forensic analysis for the same reason that any marker is useful in forensic analysis - specifically, to specifically identify individual members of the human population based on the presence or absence of the described polymorphism. Thus, the Examiner's argument does not support the alleged lack of utility. Importantly, it has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement.

Reply: While it is agreed that FDA approval is not a requirement for finding a compound patentably useful and that routine experimentation does not render an invention unpatentable, it is noted that in the instant case, the utility rejection was not applied to the claimed invention because it failed to comply with government requirements to market the invention for human consumption or because some routine experimentation is required to practice the claimed invention. Instead, the utility rejection was applied due to the lack of information as to its biological function as already discussed. The specification fails to disclose information in regard to the biological significance and further characterization of the claimed polynucleotides and the protein encoded thereby, such as (1) the type of protein being encoded by the claimed polynucleotides (i.e., transcription factor, kinase, protease, binding protein, cytoskeletal protein, receptor, hormone etc etc), (2) the biological processes or pathways in which the encoded protein set forth by SEQ ID NO: 2 are involved, (3) the type of interactions the encoded protein is involved in (i.e. binding, enzymatic, structural, signaling, etc.), and (4) how mutation of the encoded protein affects a specific cellular function or is a cause for a specific disease. As known in the art polynucleotides encode a wide variety of polypeptides with diverse functions. Since, the cellular function of the instant protein and the biochemical and pathological processes associated with the instant protein are all unknown, further research is required to identify or reasonably confirm a "real world" context of use (Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966)). In view of the extremely large amount of information unknown in regard to the claimed invention, it is not reasonable for one of skill in the art to conclude that the additional research required to practice the claimed invention is merely routine. In regard to *In re Wands*, while it is agreed that one need not to disclose what is well known in the art, it is

noted that neither the specification nor the state of the art describe or provide any information as to the actual biological function of the polypeptide encoded by the claimed polynucleotides other than to indicate that the polypeptide of the instant invention has homology to the known binding domains, thrombospondin and disintegrin, and displays similarity to the ADAMTS family of metalloproteases, receptor-linked phosphatases, and cell adhesion molecules (pg 17, line 29-pg 28, line1). As previously explained this, by itself, is insufficient to provide the skilled artisan with the knowledge of how to use the claimed polynucleotides. Since, information, which would enable one of skill in the art to practice the claimed invention, is not known in the art, it is the specification, which must provide the necessary information to enable the skilled artisan to practice the claimed invention.

(4) Although Appellants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. 101, the present sequence has a number of patentable utilities, among them, in the identification of protein coding sequence, in mapping the protein encoding regions of the corresponding human chromosome, specifically chromosome 9, in assessing gene expression patterns using high-through put DNA chips, and as targets for the discovery of drugs that are associated with human disease

The Final Action questioned these asserted utilities, stating, for example that, Applicants have also not identified any particular reason for use of this particular polynucleotide in "DNA chips". The Examiner once again seems to be confusing the requirements of a specific utility with a unique utility. Those of skill in the art would instantly recognize that the present nucleotide sequences would be an ideal, novel candidate for assessing gene expression using such DNA chips. Clearly, compositions that enhance the utility of such DNA chips, such as the

presently claimed nucleotide sequences, must in themselves be useful. Applicants point out that nucleic acid sequences are commonly used in gene chip applications without any information regarding the function of the encoded protein, or even evidence regarding whether the sequence is actually even expressed. Thus, the present sequence, which has been biologically validated to be expressed, has a much greater utility than sequences that are merely predicted to be expressed based on bioinformatic analysis. Applicants also point out that nucleic acid sequences such as SEQD NO: 2 are routinely used by companies through out the biotechnology sector exactly as they are presented in the Sequence Listing, without any further experimentation.

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. One such company, was viewed to have such "real world" value that it was acquired by large a pharmaceutical company for significant sums of money (net equity value of the transaction was $620 million). The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established.

Reply: It is noted that the specification states that the gene comprising the polynucleotide of SEQ ID NO: 1 "is apparently present on human chromosome 9" (pg 3, line 8-9) and also states said gene "is apparently present on human chromosome 12" (pg 18, line 1-2). Since the Appeal Brief use "chromosome 9", the Examiner will also. However, the above discrepancy in the specification should be corrected.

While it is agreed that the claimed polynucleotides can in fact be used in detecting the particular locus (i.e. position in the chromosome at which the gene resides) of the human genome

where the gene encoding the polypeptide of SEQ ID NO: 2 is located, such use is not considered specific for the following reasons. As known in the art, any human polynucleotide, which encodes a protein, can be used to detect the particular locus of the corresponding gene; therefore, any human polynucleotide, which encodes a protein can be used to determine the specific chromosome which contains that locus. In addition, while one could argue that the claimed polynucleotides can be used as markers to isolate the particular chromosome which contains the locus of the gene encoding the polypeptide of SEQ ID NO: 2, since that chromosome will contain many other genes, any polynucleotide which is complementary to any of those other genes will also serve as a marker for that particular chromosome. In regard to the use of the claimed polynucleotides in producing a genetic map of high resolution, which can then be used to identify specific genes involved in disease, it is noted that this use is not specific, since many other polynucleotides, which encode proteins, as indicated above, can be used in a similar way. In addition, it is noted that there is no disclosure in the specification as to any diseases, conditions, or biological changes associated with modifications in the structure (i.e. mutations) of the gene encoding the polypeptide of SEQ ID NO: 2, which would lead one of skill in the art to use the claimed polynucleotides as probes to detect mutations in that specific locus (i.e. specific markers).

While it is agreed that (1) only a small portion of the genome contains exons and (2) ESTs (expressed sequence tags) are of great significance in the analysis of genomic data specifically in the area of gene prediction and function annotation, it is unclear how the claimed polynucleotides provide biologically validated data for the following reasons. As known in the art and also discussed in Venter et al. pages 1317-1321, automated gene annotation (i.e.

computer-based annotation of function based on sequence homology) uses among other things, ESTs (partial sequences of expressed genes) as one of the tools to identify and annotate genes and their corresponding cDNAs (i.e. transcripts which encode proteins and lack introns). The information provided by ESTs along with clustered genomic sequences, and cDNAs from various tissue mRNAs were used to assemble the cDNA set forth by SEQ ID NO: 1 (specification, pg 4, lines 7-9). As such, there is no assurance that the assembled sequence encoding the polypeptide of SEQ ID NO: 2 is indeed an actual transcript of a gene since, it is known in the art that computer-based assembly of genes and their transcripts (cDNA) is not perfect and may lead to wrong splicing of genes. In fact, Venter et al., page 1320, second column, last paragraph, indicates that their annotation algorithm (Otto), in the absence of the corresponding experimental evidence, has in some cases incorrectly predicted gene splicing and the wrong transcript has been predicted. Since Appellants provide no experimental evidence to corroborate that the claimed full-length polynucleotides are indeed the actual transcripts of a gene, one cannot reasonably conclude that the claimed polynucleotides provide biologically validated data.

Appellant's arguments in regard to utility of the claimed polynucleotides in DNA chips have not been found persuasive. It is agreed that the use of polynucleotides in DNA chips (microarrays) is widespread and that the claimed polynucleotides can be attached to DNA chips. However, as indicated by the Examiner in previous Office Actions, for the claimed polynucleotides to be specifically useful in such application, one would require some knowledge or guidance as to the biological role of the polypeptide encoded by such polynucleotides to effectively use the information gathered in tracking the expression patterns of such

polynucleotides. The reduction or increase in expression of a polynucleotide is meaningless unless one can link changes in expression with some biological function. For example, if one were to use the claimed polynucleotides in assays which would lead to the discovery of drugs of a specific condition, such as an assay which uses a DNA chip to evaluate expression patterns upon exposure to a test compound, one need to know which diseases and/or biological functions are associated with the expression of such polynucleotides. Otherwise, one of skill in the art would have to carry out further experimentation to determine which are the conditions (i.e. diseases) and/or biological functions associated with the claimed polynucleotides. Appellant's asserted utility of the claimed polynucleotides as specific markers which are targets for discovering drugs associated with human disease is not a specific and substantial utility since the specification is silent in regard to (1) the conditions and/or biological functions which are associated with the expression of the claimed polynucleotides, (2) whether increase or decrease in expression correlates with disease, and (3) which levels of increase or decrease in expression of the claimed polynucleotides are indicative of the presence or absence of a disease. This is analogous to the examples provided by MPEP § 2107.01 in regard to what constitutes carrying out further research to identify or reasonably confirm a "real world" context of use since basic research is required to determine the properties or the mechanisms in which the claimed product is involved. The Examiner acknowledges the hundreds of issued patents in regard to DNA chips; however, it is noted that the instant claims are not drawn to methods of use of DNA chips or to DNA chips (microarrays) but rather to specific polynucleotides. Furthermore, the asserted use of the claimed polynucleotides in DNA chips is not specific since as Appellants have stated, many other polynucleotides including those in the public domain can and are used in DNA chips. In

regard to the argument that the claimed polynucleotides can be used as specific markers of the human genome, it is noted that there is no disclosure in the specification as to how the claimed invention is a specific marker of the human genome. This situation is analogous to the examples provided in MPEP § 2107.01 in regard to what constitute a non-specific utility since, as stated MPEP § 2107.01 "a specific utility is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to a broad class of inventions". Therefore, in view of the lack of information as to the biological function and/or condition associated with the expression of the claimed polynucleotides or how the claimed invention is a specific marker of the human genome, it is unclear how one of skill in the art can reasonably conclude that the asserted use of the claimed polynucleotides in DNA chips is a specific and substantial utility.

While it is agreed that (1) there is an industry based on the use of polynucleotides and fragments, (2) there are many billions of dollars invested in companies which use DNA chips and related technologies, (3) billions of dollars have been spent in the generation of human genomic data, and (4) the utility of human genomic data has been understood for many years, Appellant's arguments have not been found persuasive for the following reasons. First, it is noted that it is the patentable utility of the specific polynucleotides claimed in the instant application and not the general utility of DNA chips, polynucleotides or fragments, which is being determined and discussed. The Examiner is not disputing the patentable utility of DNA chips as a collection of polynucleotides linked to a solid support but rather the patentable utility of specific polynucleotides encoding the polypeptide of SEQ ID NO: 2. Furthermore, the Examiner is not disputing that one of skill in the art can see the potential usefulness of information coming out of the human genome project; however, it is also known in the art that

this information is valuable to the extent that it provides a starting point for scientists to further investigate the biological significance of the genetic information collected and possibly discover how to treat many conditions and diseases. In fact, while the potential usefulness of human genomic data was enormous, the lack of an immediate use for human genomic data was the primary reason why it was the federal government, and not a private entity, who first provided funding for the Human Genome Project. While it is agreed that the disclosure of an additional human polynucleotide provides more information in regard to the human genome, as indicated previously, in the absence of any additional information in regard to its biological function, the isolation of the human polynucleotides of the instant application is only useful as a starting point for researchers to further investigate its biological significance, therefore the utility of the instant polynucleotides, as clearly stated in MPEP § 2107.01 is not a "real world" substantial utility.

(5) Additionally, Appellants pointed out in the Response to the Final Action that two sequences sharing nearly 100% percent identity at the protein level over an extended region of the claimed sequence are present in the leading scientific repository for biological sequence data (GenBank), and have been annotated by third party scientists wholly unaffiliated with Appellants as Homo sapiens ADAMTS-like 1 variants 1 and 2 (GenBank accession numbers NM-139238 and NM-052866). The specification, as originally filed, noted the similarity of the present sequence to "matrix metalloproteases" (page 2, lines 7-8), and particularly "the ADAMTS family of metalloproteases" (page 17, lines 31-32). Furthermore, the scientists that described ADAMTS-like 1 have determined that the protein is localized to the extracellular matrix (Hirohata et al., J. Biol. Chem. 277:12182-12189, 2002; Exhibit K). Applicants respectfully point out that the legal test for utility simply involves an assessment of whether those skilled in

the art would find any of the utilities described for the invention to be believable. Given these two GenBank annotations and the manuscript by Hirohata et al., there can be no question that those skilled in the art would clearly believe that Appellants' sequence is an ADAMTS-like protease, and would thus readily understand the utility of the presently claimed sequence, as described above, particularly in gene chip applications.

Reply: It is acknowledged that the protein of SEQ ID NO: 2 has some sequence homology with "Homo sapiens ADAMTS-like 1" variants 1 and 2 (GenBank accession numbers NM-139238 and NM-052866). However, a conclusion that the protein of SEQ ID NO: 2 is a metalloproteases cannot be deduced from said homology; since, only the first 30% of SEQ ID NO: 2 has homology with ADAMTS-like 1, and this N-terminal 30% of SEQ ID NO: 2 does not include a catalytic domain. Furthermore, SEQ ID NO: 2 does not contain the conserved His-Glu-Xxx-Xxx-His-Xxx-Xxx-His motif for the catalytic domain of metalloproteases (Fahrenholz et al, 2000). SEQ ID NO: 2 also lacks the Pro-Arg-Cys-Gly-Xxx-Pro motif for the propeptide domain of metalloproteases (Massova et al, 1998). Sequence searches showed no consistent homology for the full-length SEQ ID NO: 2 with metalloproteases. One polynucleotide sequence showing high homology to SEQ ID NO: 1, 98% over the full-length of SEQ ID NO: 1, encodes a thrombospondin-like protein (WO200121658-A1 SEQ ID NO: 18; Gene #8; p26-30 and Figs 4-5). A second polynucleotide sequence showing high homology to SEQ ID NO: 1, 98% over the full-length of SEQ ID NO: 1, encodes a hypothetical protein from C. elegans of unknown function that is not a metalloprotease (WO200154474-A2 SEQ ID NO: 134; Gene #124; Table 1 p76 and Table 2 p226). A third protein, TANGO 224, has a thrombospondin domain but is not a metalloprotease (WO200039284-A1 SEQ ID NO: 224; Abstract and pages

52-56). Thus, the identity of the polynucleotide sequence of SEQ ID NO: 1, or any other polynucleotide sequence encoding the protein of SEQ ID NO: 2, as encoding a metalloprotease is not supported.

(6) Appellants argue (pg 13, parg 3-pg 12, parg 1) that the Federal Circuit in *Juicy Whip Inc. v. Orange Bang, Inc.* has stated that the threshold of utility is not high and that an invention is useful under section § 101 if it is capable of providing some identifiable benefit. Appellants further cite *Brooktree Corp. v. Advanced Micro Devices, Inc.* to indicate that the Federal Circuit has stated that a claimed device must be totally incapable of achieving a useful result to lack utility under 35 USC § 101. Appellants cite *Cross v. Iizuka* in support of the argument that any utility for a claimed invention is sufficient to satisfy the requirements of 35 USC § 101 and indicate that the Federal Circuit has confirmed that anything under the sun made by man is patentable in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*

Reply: The Examiner acknowledges the cases cited by Appellants wherein issues in regard to 35 USC § 101 were examined. It is noted however that only *Cross v. Iizuka* is considered relevant to the instant discussion since, the inventions in that case are chemical compounds. In *Juicy Whip Inc. v. Orange Bang, Inc.*, the issue of utility was discussed in regard to a juice dispenser, *in Brooktree Corp. v. Advanced Micro Devices, Inc.*, the issue of utility was discussed in regard to a digital to analog conversion circuitry, and in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, the issue of utility was discussed in regard to a business method.

In *Cross v Iizuka*, the issues which the Federal Circuit had to examine were whether the Board erred in finding that the utility disclosed in the Japanese priority application by Iizuka was

sufficient to meet the practical utility requirement of 35 U.S.C. §101 and whether the Board erred in finding that the Japanese priority application contained sufficient disclosure to satisfy the enablement, i.e., how-to-use, requirement of 35 U.S.C. § 112. The PTO, the Board of Patent Appeals and Interferences and the Federal Circuit found that the claimed imidazole derivative compounds had practical *in vitro* utility since in addition to the disclosure of the structure of the claimed imidazole derivative compounds, there was experimental evidence of the strong inhibition of thromboxane synthetase by these imidazole derivatives in human and bovine microsomes. Thromboxane synthetase is an enzyme which leads to the formation of thromboxane A2, which at the time the applications of Cross and Iizuka were filed, was postulated to be a causal factor in platelet aggregation, which in turn, is known to be associated with platelet thrombosis, pulmonary vasoconstriction or vasospasm, inflammation, hypertension, and collagen-induced thrombosis. In contrast, the instant application discloses the structure of the claimed polynucleotides and no biological characterization of the polypeptide encoded by the claimed polynucleotides other than to state that based on sequence homology, it appears to have thrombospondin and disintegrin domains, and particular structural similarity to the ADAMTS family of metalloproteases as well as displaying similarity to receptor-linked phosphatases and membrane associated cell adhesion proteins (pg 17, line 29-pg 18, line 1). For the reasons indicated above, even if one assumes that the polypeptide encoded by the claimed polynucleotides is, for example, a metalloprotease, the specification fails to provide sufficient information for one of skill in the art to know how to use the claimed invention. The specification is silent in regard to (1) the substrate of said metalloprotease, (2) the biological processes or pathways in which said metalloprotease are involved, (3) the types of interactions

said metalloprotease involved in (i.e. binding, enzymatic, structural, signaling, etc.), and (4) how mutation of said metalloprotease affects a specific cellular function or is a cause for a specific disease. Information in regard to biological function is essential for the asserted utility in DNA chips to be specific and substantial, for the reasons already discussed above. While one of skill in the art can reasonably conclude that the chemical compounds of Iizuka had a credible, specific and substantial utility, i.e. the imidazole derivative compounds inhibit an specific enzyme, thromboxane synthetase, in human and bovine microsomes, a skilled artisan cannot reasonably conclude that the claimed polynucleotides have a specific and substantial, or even credible utility in view of the evidence presented.

(7) Finally, while Appellants are well aware of the new Utility Guidelines set forth by the USPTO, Appellants respectfully point out that the current rules and regulations regarding the examination of patent applications is and always has been the patent laws as set forth in 35 U.S.C. and the patent rules as set forth in 37 C.F.R., not the Manual of Patent Examination Procedure or particular guidelines for patent examination set forth by the USPTO. Furthermore, it is the job of the judiciary, not the USPTO, to interpret these laws and rules. Appellants are unaware of any significant recent changes in either 35U.S.C. 101, or in the interpretation of 35U.S.C. 101 by the Supreme Court or the Federal Circuit that is in keeping with the new Utility Guidelines set forth by the USPTO.

Reply: Appellants are reminded that the Examiner must examine a patent application according to the guidelines set forth by the USPTO as well as the MPEP, since the Examiner has no authority to disregard such guidelines or to apply her own interpretation of patent law in the examination of the application. Furthermore, as set forth in the guidelines and the MPEP, the

guidelines were promulgated by the PTO in accordance with all applicable case law and thus are believed to be consistent therewith. While the Examiner acknowledges the US patents SN5,817,479, SN5,654,173, SN5,552,281 and SN6,340,583, each application is examined on its own merits according to the current guidelines of examination as set forth by the USPTO and a discussion on the utility of any polynucleotide claimed in such patents would require a detailed review of the record of each individual case, which would be improper herein. Finally, Appellants are further reminded that the Examiner has no authority to comment in regard to the legality of the new utility guidelines or the MPEP as set forth by the USPTO.

B. Are Claims 1-4 Unusable Due to a Lack of Patentable Utility?

The Final Action next rejects claims 1-4 under35U.S.C. 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility.

The arguments detailed above in Section VIII(A) concerning the utility of the presently claimed sequences are incorporated herein by reference. As the Federal Circuit and its predecessor have determined that the utility requirement of Section 101 and the how to use requirement of Section 112, that paragraph, have the same basis, specifically the disclosure of credible utility, Appellants submit that as claims 1-4 have been shown to have "a specific, substantial, and credible utility", as detailed in Section VIII(A) above, the present rejection of claims 1-4 under 35 U.S.C. j 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-4 under35U.S.C. 112, first paragraph, must be overruled.

Reply: As indicated by Appellants, a rejection under § 112, first paragraph, may be affirmed on the same basis as a lack of utility rejection under § 101. *See, e.g., In re Swartz*, 56 USPQ2d 1703 (Fed. Cir. 2000); *In re Kirk*, 153 USPQ 48 (CCPA 1967).

Appellants arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of lack of utility for the reasons out lined above. Therefore, for reasons set forth above, it is believed that rejections under 35 USC § 101 and 35 USC § 112, first paragraph, should be sustained.

Respectfully submitted,

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